

Exhibit G

The Pseudotumor Cerebri Syndrome

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KEYWORDS

- Pseudotumor cerebri • Idiopathic intracranial hypertension • Papilledema
- Cerebrospinal fluid

KEY POINTS

- The pseudotumor cerebri syndrome (PTCS) may be primary (idiopathic intracranial hypertension, IIH) or arise from a secondary cause.
- PTCS is an important cause of new daily persistent headaches and may lead to permanent visual loss if untreated. Papilledema is the hallmark of PTCS and is required to make a definite diagnosis, emphasizing the importance of a funduscopic examination on all patients with new or unexplained headaches.
- PTCS affects boys and girls equally until puberty, when the incidence in girls increases markedly. IIH in adults is almost exclusively a disease of overweight women of child-bearing age.
- A high opening pressure on a lumbar puncture is not adequate to make the diagnosis of PTCS if papilledema is absent.
- Treatments for PTCS include treating the secondary cause (if present), weight loss, medications, and surgery. Repeated lumbar punctures are helpful to control the pressure urgently while awaiting surgery, during pregnancy, and for infrequent relapses.
- The main goal of treatment is to preserve or restore vision; careful ophthalmologic follow-up with perimetry is necessary.
- Headache treatment may be independent of therapies to address intracranial hypertension.

INTRODUCTION

The pseudotumor cerebri syndrome (PTCS) is a perplexing syndrome of increased intracranial pressure without a space-occupying lesion. The terminology for the disorder has changed over the years and the diagnostic criteria were revised to reflect

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advances in diagnostic technology and new insights into the disease process.¹ The classification and nomenclature depend on the presence or absence of an underlying cause. When the diagnostic criteria are followed, an alternative diagnosis is unlikely (Box 1). When no secondary cause is identified, the syndrome is termed "Idiopathic Intracranial Hypertension (IIH)." An accurate diagnosis is imperative to initiating appropriate treatment, which may incorporate medical or surgical modalities. The main goal of therapy is the preservation of vision.

EPIDEMIOLOGY

Incidence studies from various countries estimate the annual incidence of pseudotumor cerebri syndrome (PTCS) as 0.9/100,000 in the general population, rising to 3.5/100,000 in women 15 to 44 years and 19.3/100,000 in women ages 20 to 44 years who weigh 20% or more than their ideal body weight.²⁻⁵ Some of the patients included in those studies had an identifiable secondary cause; the statistics are not strictly applicable to the idiopathic form. However, the incidence is rising, which may be attributed to improved recognition and the obesity epidemic.⁶ After puberty, the disorder affects women 9 times as often as men. Boys and girls are equally affected before puberty.⁷⁻¹⁰ When the diagnostic criteria are strictly applied in patients over the age of 18 years, the idiopathic form occurs almost exclusively in women. It rarely develops in patients over age 45 years.¹¹

Box 1

Diagnostic criteria for PTCS

A diagnosis of PTCS is "definite" if the patient fulfills criteria A–E. The diagnosis is considered "probable" if criteria A–D are met but the measured CSF pressure is lower than specified for a "definite" diagnosis.

1. Required for diagnosis of the pseudotumor cerebri syndrome

- A. Papilledema
- B. Normal neurologic examination except for cranial nerve abnormalities
- C. Neuro-imaging: Normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (female and obese), and MRI, with and without gadolinium, and magnetic resonance venography for others. If MRI is unavailable or contraindicated, contrast-enhanced CT may be used.
- D. Normal CSF composition
- E. Elevated LP opening pressure (>250 mm CSF in adults and >280 mm CSF in children [250 mm CSF if the child is not sedated and not obese]) in a properly performed LP.

2. Diagnosis of PTCS without papilledema

- In the absence of papilledema, a diagnosis of PTCS can be made if B–E are satisfied, and in addition, the patient has a unilateral or bilateral abducens nerve palsy.
- In the absence of papilledema or sixth nerve palsy, a diagnosis of PTCS can be "suggested" but not made if B–E are satisfied, and in addition, at least 3 of the following neuroimaging criteria are satisfied:
 - i. Empty sella
 - ii. Flattening of the posterior aspect of the globe
 - iii. Distention of the perioptic subarachnoid space with or without a tortuous optic nerve
 - iv. Transverse venous sinus stenosis

SYMPTOMS***Headache***

Almost all patients with PTCS have headache, which is the most common presenting symptom.¹²⁻¹⁴ Occasionally patients are asymptomatic¹³ and seek medical attention when papilledema is detected on a routine eye examination.¹⁵ There are no specific distinguishing characteristics of the headache, which is often daily, bilateral, frontal, or retroocular.^{13,16} It is usually moderate to severe in intensity and some patients describe increased severity on awakening. The headache may also be throbbing, with nausea, vomiting, and photophobia, resembling migraine. Neck and back pain are often prominent features.^{13,17} It is not unusual for patients with PTCS to have coexisting migraine headaches, making the diagnosis difficult unless other signs are present.^{18,19} PTCS is in the differential diagnosis of new daily persistent headache. The presence of chronic daily headaches raises the possibility of medication overuse headache (MOH), which occurs in PTCS patients, particularly in the chronic stages. Analgesic overuse may worsen an unrelated primary headache disorder and simulates "IIH without papilledema" (IIHWOP).²⁰

Transient Visual Obscurations

Although not specific for PTCS, transient obscurations of vision are most commonly experienced in this disorder and are sometimes the presenting symptom. They likely are a manifestation of disc edema leading to transient ischemia of the optic nerve head.²¹ Patients describe brief episodes of monocular or binocular visual loss that may be partial or complete. The obscurations are present in about 70% of PTCS patients, typically last seconds, and do not correlate with the degree of disc edema or visual loss.^{22,23}

Pulsatile Tinnitus

Pulsatile tinnitus occurs in 60% of patients and 9% of controls.¹⁶ Patients should be queried about this symptom because it is often not volunteered. The noises may be unilateral or bilateral, often described as a heartbeat or whooshing sound. They are often abolished with a lumbar puncture (LP) or jugular venous compression.²⁴ Intracranial noises have been attributed to transmission of intensified vascular pulsations via cerebrospinal fluid (CSF) under high pressure to the walls of the venous sinuses, converting laminar to turbulent flow.²⁵ Others postulate that the endolymphatic duct may transmit pressure sensations from the CSF to the endolymph of the membranous labyrinth.²⁶ Hearing loss or a "high-altitude" sensation are also described.^{27,28}

Visual Loss

A small percentage of patients experience subjective visual loss as the initial symptom of PTCS.²² They may report blurred vision, a dark spot temporally that correlates with enlargement of the physiologic blind spot, or tunnel vision. In severe cases, profound visual loss or complete blindness occurs. The tempo of visual loss is variable in PTCS, but rapid deterioration may occur over days in severe cases. Early loss of central vision is a worrisome sign.

Diplopia

Diplopia is a frequently reported symptom in PTCS, occurring in one-third to two-thirds of patients at presentation.^{13,22} It is usually binocular and horizontal, resulting from a unilateral or bilateral abducens paresis. Binocular diplopia almost always

resolves when the intracranial pressure is normalized. Monocular diplopia or distorted vision may arise from macular edema or exudates in the setting of severe papilledema.

Other Symptoms

Minor symptoms of PTCS include radicular pain, paresthesias, neck stiffness, arthralgias of the shoulders, wrists, and knees, ataxia, and facial palsy.^{13,17,29–32} Depression and anxiety are more common in patients with PTCS than in obese or normal weight control subjects.³³ It is uncertain whether the depression results from having PTCS, or whether there is a common pathogenesis in some patients.³⁴ Occasionally depression is the initial symptom.³⁴ Complaints of impaired concentration and memory are common; cognitive decline may be related the disorder itself, chronic headaches, visual impairment, fear of blindness, depression, anger, and anxiety.³⁵

SIGNS

Papilledema

The hallmark of PTCS is papilledema that may be asymmetric or occasionally unilateral.³⁶ If stereoscopic viewing and fluorescein angiography show no evidence of papilledema, prolonged intracranial pressure monitoring is occasionally used for diagnosis.³⁷ Although there is an association between visual loss and high-grade papilledema,^{36,38} the appearance of the optic nerves does not predict visual outcome in an individual patient.³⁹ Early or mild papilledema may be difficult to detect with the direct ophthalmoscope, and stereoscopic viewing of the optic discs with indirect ophthalmoscopy is recommended. Stereoscopic fundus photography and fluorescein angiography may be helpful to determine the presence of subtle papilledema, but treatment should not be based on the appearance of the optic nerves alone. Rarely, increased intracranial pressure results in retinal choroidal folds with little to no papilledema.⁴⁰

Because the severity of papilledema influences the overall treatment strategy, it is useful to have a standardized papilledema grading system. The Frisén scale describes papilledema in stages that are clinically meaningful in the acute and subacute stages (**Box 2**).⁴¹ Early papilledema is characterized by disruption of the normal radial nerve fiber layer arrangement with grayish opacity accentuating the nerve fiber bundles. A subtle gray peripapillary halo is apparent with the indirect ophthalmoscope (**Figs. 1 and 2**). There may be concentric or retinochoroidal folds. As the papilledema grade increases, the borders of the optic disc become indistinct, with progressive elevation of the disc margins. The nerve head diameter increases and the edematous nerve fiber layer obscures one or more segments of major blood vessels leaving the disc (**Figs. 3 and 4**). With severe papilledema, the optic nerve protrudes, the peripapillary halo becomes more demarcated, and the optic cup is obliterated (**Figs. 5 and 6**). Hyperemia, vessel tortuosity, hemorrhages, exudates, nerve fiber layer infarcts (cotton wool spots), and optic nerve pallor are often observed but are too variable to use for staging purposes (**Fig. 7**).⁴¹ Papilledema will not develop in the setting of optic atrophy, which is an important consideration when considering recurrence.

It is important to differentiate true papilledema from pseudopapilledema caused by optic disc drusen, tilted optic discs, or a myelinated nerve fiber layer (**Figs. 8–10**). Stereoscopic viewing of the fundus can usually distinguish these entities. Optic disc drusen may also cause transient visual obscurations²¹ and can easily be confused with PTCS, particularly with direct ophthalmoscopy. Rarely, optic nerve drusen and PTCS coexist.⁴² This diagnostic dilemma is resolved with ultrasonography of the optic

Box 2**Papilledema grading system (Frisén scale)****Stage 0: Normal optic disc**

- A. Blurring of nasal, superior, and inferior poles in inverse proportion to disc diameter
- B. Radial nerve fiber layer (NFL) without NFL tortuosity
- C. Rare obscuration of a major vessel, usually on the upper pole

Stage 1: Very early papilledema

- A. Obscuration of the nasal border of the disc
- B. No elevation of disc borders
- C. Disruption of the normal radial NFL arrangement with grayish opacity accentuating nerve fiber bundles
- D. Normal temporal disc margin
- E. Subtle grayish halo with temporal gap (best seen with indirect ophthalmoscope)
- F. Concentric or radial retinochoroidal folds

Stage 2: Early papilledema

- A. Obscuration of all borders
- B. Elevation of the nasal border
- C. Complete peripapillary halo

Stage 3: Moderate papilledema

- A. Obscuration of all borders
- B. Elevation of all borders
- C. Increased diameter of the optic nerve head
- D. Obscuration of one or more segments of major blood vessels leaving the disc
- E. Peripapillary halo: irregular outer fringe with fingerlike extensions

Stage 4: Marked papilledema

- A. Elevation of entire nerve head
- B. Obscuration of all borders
- C. Peripapillary halo
- D. Total obscuration on the disc of a segment of a major blood vessel

Stage 5: Severe papilledema

- A. Dome-shaped protrusions, representing anterior expansion of the optic nerve head
- B. Peripapillary halo is narrow and smoothly demarcated
- C. Total obscuration of a segment of a major blood vessel may or may not be present
- D. Obliteration of the optic cup

From Frisén L. Swelling of the optic nerve head: a staging scheme. J Neurol Neurosurg Psychiatry 1982;45:13–8; with permission.

nerves. Drusen are visualized as highly reflective areas on the optic nerve head, whereas the 30° tilt test demonstrates a distended optic nerve sheath with papilledema. High-resolution computed tomography (CT) scanning of the orbits often demonstrates calcified drusen that may be buried behind the optic nerve papilla.



Fig. 1. Normal (stage 0) optic nerve. There is no peripapillary halo, obscuration of a major vessel crossing the disc margin, or disruption of the retinal nerve fiber layer. This patient has no physiologic cup, a normal variant. (Courtesy of IIHTT Photography Reading Center, Rochester, NY.)

Loss of spontaneous venous pulsations is often used to gauge intracranial pressure. Spontaneous venous pulsations typically disappear if CSF pressure is greater than 250 mm, and their presence generally indicates that the CSF pressure at the time is 190 mm or less.^{43,44} However, because many normal individuals lack spontaneous venous pulsations, it is not a reliable sign unless venous pulsations were previously observed in a particular patient.

Papilledema may not be present very early in the course of the disease or there is pre-existing optic atrophy. Gliotic changes in the retinal nerve fiber layer may preclude the development of papilledema in patients having a relapse of the disease.

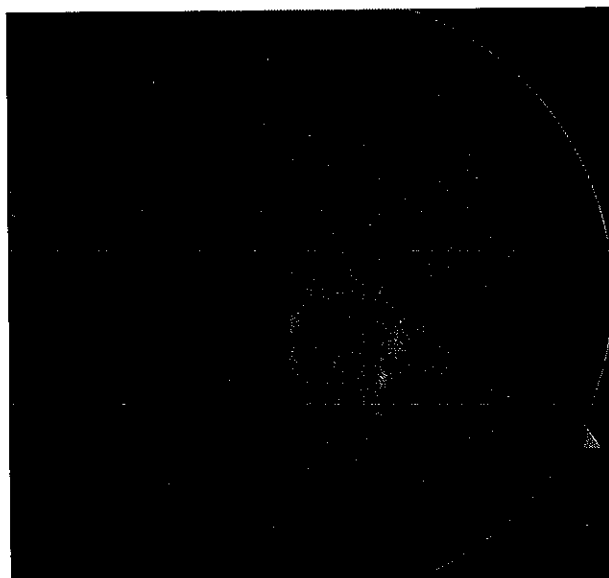


Fig. 2. Stage 1 papilledema. Note the C-shaped halo with a temporal gap. There is disruption of the normal retinal nerve fiber layer and a normal temporal disc margin. (Courtesy of IIHTT Photography Reading Center, Rochester, NY.)

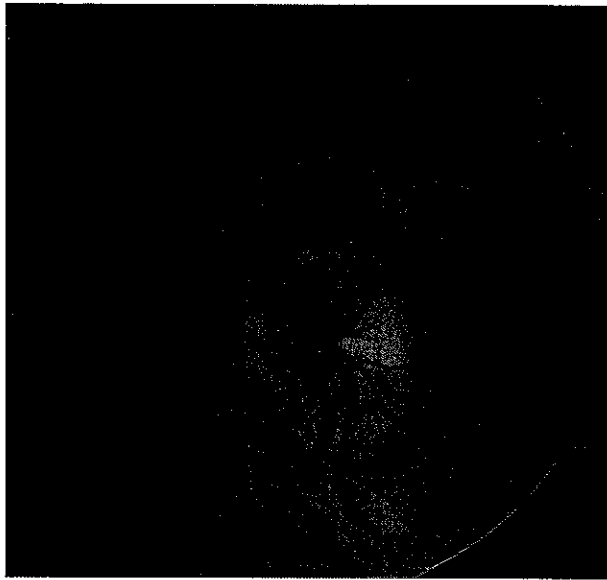


Fig. 3. Elevation of the nasal optic disc border with no major vessel obscuration and a circumferential peripapillary halo are characteristics of stage 2 papilledema. (Courtesy of IIHTT Photography Reading Center, Rochester, NY.)

Visual Acuity and Optic Nerve Function Tests

Early papilledema is typically associated with normal or near-normal Snellen visual acuity. In severe cases of pseudotumor cerebri, the acuity may deteriorate rapidly as the optic nerve becomes ischemic. Approximately 15% of patients have visual acuities worse than 20/20 at the initial visit; it is this author's experience that decreased visual acuity at presentation often portends a poor prognosis.^{13,22} Because Snellen

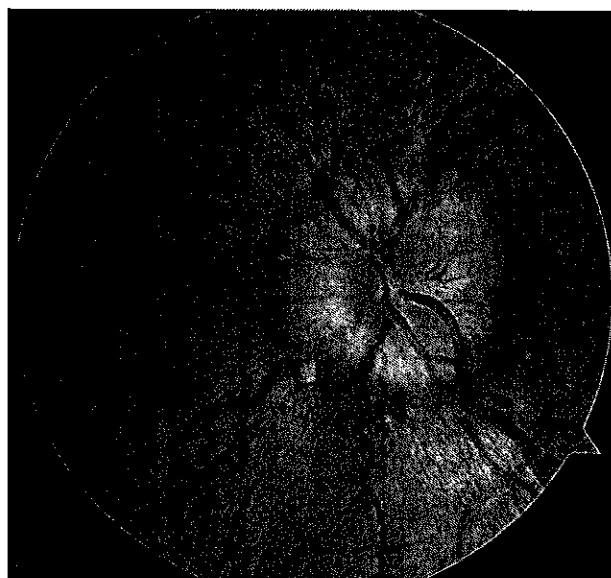


Fig. 4. Obscuration of one or more segments of a major blood vessel leaving the disc margin and elevation of all optic disc borders are seen in stage 3 papilledema. The outer fringe of the peripapillary halo is irregular with fingerlike extensions. (Courtesy of IIHTT Photography Reading Center, Rochester, NY.)

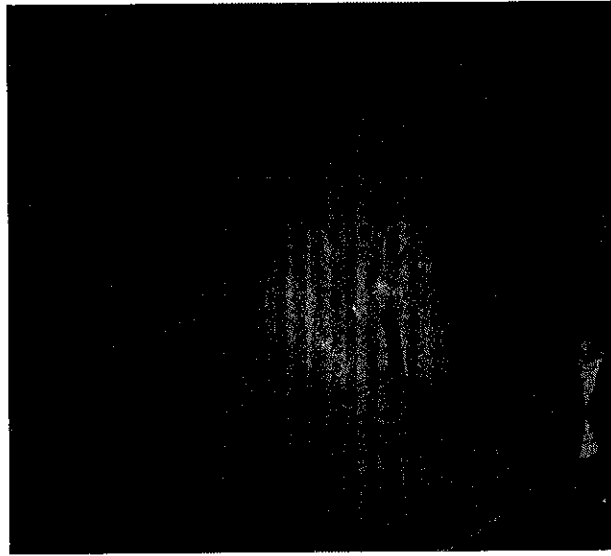


Fig. 5. Stage 4 papilledema. There is total obscuration of a major vessel on the optic disc with elevation of the entire optic nerve head and a complete peripapillary halo. (Courtesy of IIHTT Photography Reading Center, Rochester, NY.)

visual acuity is not sensitive to visual loss found on perimetry, it should not be used as the sole indicator of visual function.³⁹

Contrast sensitivity is a sensitive and early indicator of optic nerve dysfunction in PTCS. Low-, middle-, and high-frequency loss has been reported.^{45,46} However, contrast sensitivity has not proved to be as useful as perimetry in the assessment patients with PTCS. Color vision testing is insensitive for visual loss.¹³ There is no role for visual-evoked potentials in this disorder; they are unreliable and remain normal until substantial vision is lost.⁴⁵ The presence of a relative afferent pupillary defect indicates asymmetric visual loss and is uncommonly present, as the optic neuropathy of PTCS is most often symmetric.^{22,39}

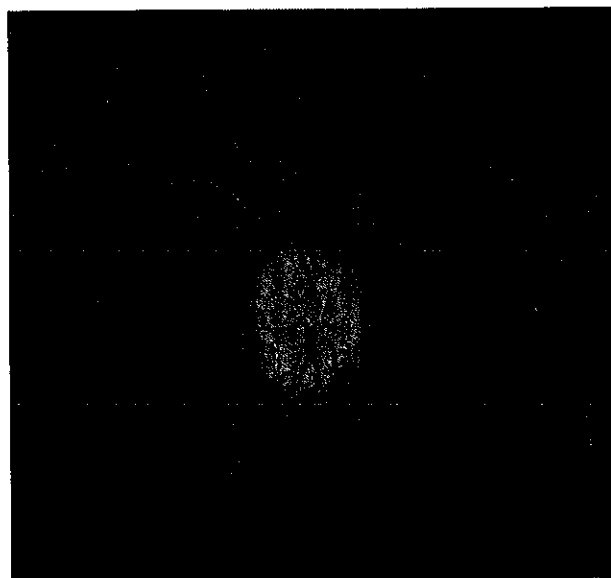


Fig. 6. Partial obscuration of all vessels leaving the disc and at least one vessel on the disc with diffuse optic nerve elevation and a complete peripapillary halo define stage 5 papilledema. (Courtesy of IIHTT Photography Reading Center, Rochester, NY.)

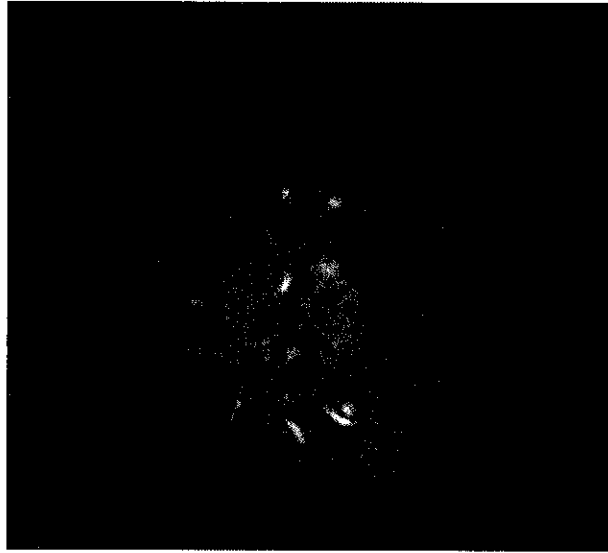


Fig. 7. Stage 4 papilledema with retinal exudates. (Courtesy of IIHTT Photography Reading Center, Rochester, NY.)

Perimetry

The most useful test for evaluating visual function in patients with PTCS is perimetry. The visual field defects are similar to those in other causes of papilledema and are characteristic of optic nerve dysfunction. Goldmann or automated threshold perimetry is required for adequate assessment. One study showed enlargement of the blind spot, representing papilledema, in 96% of patients by Goldmann perimetry and 92% of patients with automated perimetry.³⁹

Other visual field defects include inferonasal loss and generalized constriction (Figs. 11 and 12). Occasionally it is difficult to distinguish genuine visual field constriction

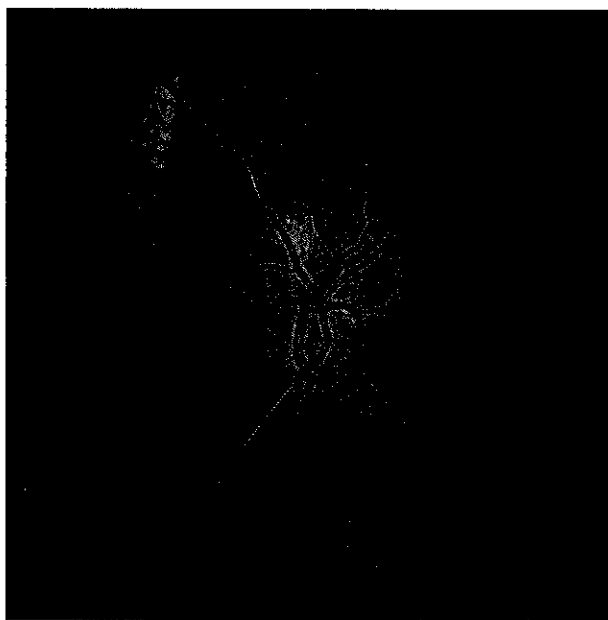


Fig. 8. The "lumpy-bumpy" irregular contour of optic disc drusen may simulate papilledema. (Courtesy of Valerie Biousse, MD, Atlanta, GA.)



Fig. 9. Myelinated optic nerve fibers. The optic disc is surrounded inferiorly by myelinated, feathery nerve fibers. (Courtesy of Anil D. Patel, MD, FRCSC, FACS, Oklahoma City, OK.)

from functional (nonorganic) visual loss.^{47,48} Central, paracentral, arcuate, and altitudinal scotomas may occur. The visual field loss may be severe, leading to blindness.²² The most frequently detected visual field abnormalities in 50 PTCS patients prospectively evaluated with automated and Goldmann perimetry were blind spot enlargement, generalized field constriction, and nasal defects.¹³

Ocular Motility Abnormalities

Unilateral or bilateral lateral rectus palsy is a nonlocalizing sign of increased intracranial pressure. It typically produces binocular, horizontal diplopia, and an esotropia may be detected. Vertical diplopia from a skew deviation or fourth nerve palsy is uncommon.⁴⁹⁻⁵¹ Global ophthalmoparesis is rare and generally indicates the presence

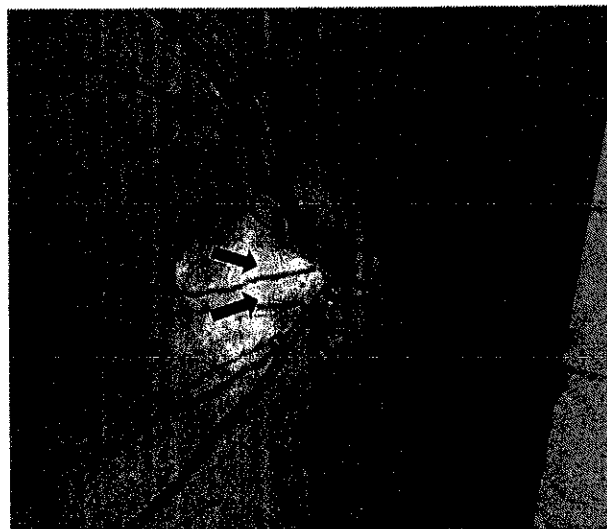


Fig. 10. Tilted optic discs may mimic optic disc edema. The nasal portion of the optic disc is markedly elevated compared with the temporal portion with temporal peripapillary atrophy. (arrows) Temporal margin of the optic disc.

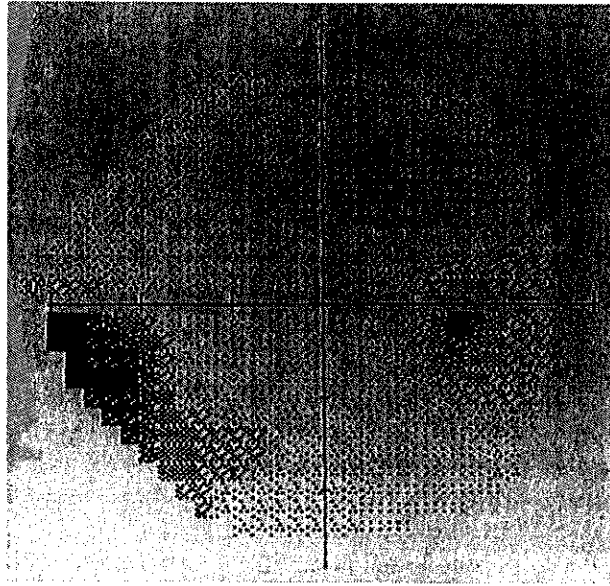


Fig. 11. Automated threshold perimetry (Humphrey Instruments, Allergan-Humphrey, San Leandro, CA, USA) of the central 24° shows an enlarged blind spot and inferonasal depression in a patient with pseudotumor cerebri and mild papilledema. (From Friedman DI. Pseudotumor cerebri. *Neurosurg Clin North Am* 1999;10:612; with permission.)

of an underlying disorder such as venous sinus occlusive disease.^{52,53} The ocular motor paresis resolves when the intracranial pressure is lowered.⁵²

Neuroimaging

Neuroimaging is mandatory before the performance of an LP to exclude a space-occupying lesion or ventriculomegaly. Although early studies with CT described small

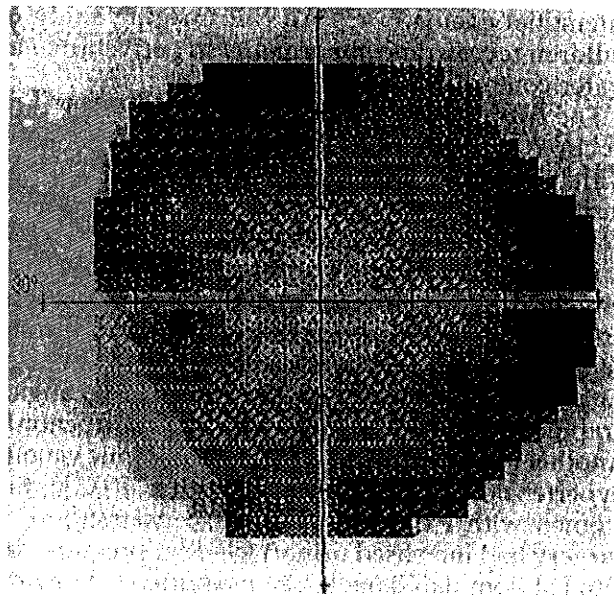


Fig. 12. Automated threshold perimetry (Humphrey Instruments, Allergan-Humphrey, San Leandro, CA, USA) of the central 24° reveals a diffuse reduction in sensitivity with marked generalized constriction of the visual field. Nonphysiological visual field loss may cause a similar pattern of visual field loss and must be excluded. (From Friedman DI. Pseudotumor cerebri. *Neurosurg Clin North Am* 1999;10:613; with permission.)

“slit-like” ventricles,⁵⁴ a subsequent study showed no difference in ventricular size between patients and controls.⁵⁵ Other reported abnormalities include dilated optic nerve sheaths, an empty sella (Fig. 13), and enlargement of the subarachnoid space.^{56,57} Sellar contents may revert to a normal appearance with correction of the intracranial pressure.⁵⁸ The optic nerve can be clearly differentiated from the sheath on high-resolution orbital magnetic resonance imaging (MRI) with dilation of the perineuronal subarachnoid space.^{57,59} Protrusion of the optic papilla into the posterior aspect of the globe and flattening of the posterior sclera may be seen.^{57,59,60} A small percentage of patients also have a Chiari I malformation that may be coincidental.⁶¹

MRI is the preferred imaging study in patients with suspected PTCS. If there is concern about a meningeal process or a subtle intraparenchymal lesion producing increased intracranial pressure, contrast enhancement is needed. A normal plain CT scan can be misleading. If MRI is not possible because of availability or the patient's weight, a CT scan with contrast is recommended.

Cerebral venous sinus abnormalities are often detected in PTCS patients. If the patient is taking oral contraceptives, is postpartum, or has a known coagulopathy, then a magnetic resonance venogram is indicated to search for a cerebral venous thrombosis.⁶² However, magnetic resonance venography and catheter angiography sometimes fail to detect subtle cerebral venous thrombosis.^{63,64} Venous sinus stenosis may be present in the absence of thrombosis. Elliptic-centric-ordered 3-dimensional gadolinium-enhanced magnetic resonance venography increases the ability to detect intracranial sinovenous stenosis.⁶⁵ The transverse sinuses are typically affected with smooth-walled stenosis, or flow voids from enlarged arachnoid granulations.⁶⁶ Transverse sinus stenosis is most commonly a result of increased ICP, reversing with LP or shunting, but it may be a primary finding.^{66,67} “Atypical” patients, including men, children, and slim women, should be thoroughly evaluated for an underlying cause. Contrast-enhanced MRI and magnetic resonance venography are recommended in these cases; digital subtraction angiography with venous phase imaging may also be necessary.

CSF Examination

The spinal fluid examination is critical for diagnosing PTCS. No patient should be diagnosed presumptively without a LP. There are several confounding conditions that may simulate PTCS: (1) patients with optic disc drusen or other congenital optic disc anomalies with or without chronic daily headaches; (2) central nervous system



Fig. 13. Sagittal brain MRI shows an empty sella (arrow).

infections or malignancy producing increased intracranial pressure; (3) infiltrative optic neuropathies. The LP is crucial to document elevated CSF pressure and assure normal CSF contents.

The accepted value of CSF pressure for diagnosing PTCS in adults is greater than 250 mm of water in adults; values of 201 to 249 are nondiagnostic. The CSF pressure required for diagnosis in children and adolescents is 280 mm CSF (250 mm CSF if the child is not sedated and not obese).⁶⁸ As spinal fluid pressure fluctuates, the LP may need to be repeated if the clinical suspicion is high but the pressure is normal.⁶⁹ Occasionally prolonged intracranial monitoring is needed.³⁷

Many patients with PTCS are obese, making the procedure of LP technically challenging. The patient's pressure must be measured in the lateral decubitus position with the legs relaxed. An 18- to 20-gauge spinal needle is preferred for resilience and optimal CSF flow. The clinician should be aware that pressures recorded in the sitting position are not accurate. Measurements in the prone position (ie, under fluoroscopy) are acceptable as long as the base of the manometer is at the level of the right atrium. Alternatively, the subarachnoid space may be entered with the patient in the sitting or prone position and the patient then carefully repositioned into the lateral decubitus position. If a patient is nervous or in pain during the procedure, which may require several attempts, the intracranial pressure will increase; a Valsalva maneuver can double the measured pressure.⁷⁰⁻⁷² Administration of an anxiolytic agent, such as diazepam or zolpidem tartrate, before the LP is often very helpful. Sedation and general anesthesia are to be avoided, as the decreased respiratory rate and resulting hypercapnia increase the CSF pressure.⁷³ The spinal fluid should be analyzed for glucose, protein, cell count, bacterial, fungal, and tuberculosis cultures, and cytology during the diagnostic evaluation. A therapeutic, "large-volume" spinal tap (removal of more than 20 cc of fluid) is sometimes used, although of uncertain value. Patients with PTCS are not protected against postspinal headaches.

PATHOPHYSIOLOGY

Over one hundred years after its original description by Quincke, the pathogenesis of PTCS is still uncertain.⁷⁴ Any proposed mechanism must explain the (1) lack of ventriculomegaly, (2) predilection of IIH in young, obese women, and (3) induction of PTCS by various medications, including tetracyclines and vitamin A.

Interstitial cerebral edema, increasing brain compliance and preventing hydrocephalus, was originally postulated based on a brain specimen obtained during subtemporal decompression,⁷⁵ but contradictory evidence emerged with the subsequent review of the original histologic slides and evaluation of postmortem tissue of 2 additional patients with PTCS who died of other causes. The original findings were thought to be a fixation artifact.⁷⁶

Either increased CSF production or decreased CSF absorption could produce PTCS. The most widely accepted theory postulates impaired CSF absorption at the level of the arachnoid granulations⁷⁷ or the olfactory lymphatics.⁷⁸ Impaired CSF absorption also occurs in the presence of intracranial venous hypertension and is proposed as a unifying hypothesis of PTCS.^{79,80} Cerebral venous sinus thrombosis may present solely as PTCS without impaired consciousness or lateralizing signs.⁸¹⁻⁸³ Transverse sinus stenosis, a frequent finding in IIH, has also been detected by magnetic resonance venogram in patients with chronic daily headaches, no papilledema, and normal to elevated CSF pressure.⁸⁴ Venous manometry and cervical spinal fluid pressure were recorded simultaneously in PTCS and found to have a reciprocal relationship.⁸⁰ Elevated cerebral venous sinus pressure would explain the lack of

ventriculomegaly in PTCS, because the total fluid volume within the cranial vault remains constant when either component (CSF or blood) is altered. Conversely, cerebral venous hypertension may be the response to elevated CSF pressure rather than the cause of it.⁸⁵ The near-instantaneous lowering of cerebral venous pressure with CSF removal may explain why some patients are “cured” after their diagnostic LP.

Central obesity leading to raised intra-abdominal filling pressure, increased cardiac filling pressure, and decreased venous return from the brain causing increased intracranial pressure was proposed but unsubstantiated.⁸⁶

Because the choroid plexus, the site of CSF production, is largely regulated by the sympathetic nervous system and neuroendocrine signaling, neurotransmitter abnormalities could result in abnormal spinal fluid production.^{87–91} Serotonin and norepinephrine are important in this regard. The choroid plexus contains the highest density of serotonin 5-HT_{1C} receptors in the brain, with levels 10-fold higher than other brain regions.^{92,93} CSF production by the choroid plexus can be affected by varying the levels of serotonin and norepinephrine in the central nervous system in animal studies. Pharmacologically increasing the levels of serotonin norepinephrine produces a decline in CSF production,^{88,89,94} raising the possibility that patients with IIH have abnormal norepinephrine and serotonin regulation.⁹⁵ Abnormally low serotonin levels might account for the increased CSF pressure (via increased production) as well as the high incidence of depression, anxiety, and obesity among these patients.

Understanding the mechanism whereby exogenous agents produce PTCS may provide additional insights into the pathogenesis of the disorder. For example, vitamin A intoxication is a well-established cause of PTCS. Its mechanism of action in this regard is uncertain but may be related to a toxic effect on cell membranes when the capacity of retinal binding protein is exceeded.⁹⁶ Aquaporins are a family of regulatory membrane water channel proteins that participate in the secretion and reabsorption of CSF.^{97–99} Aquaporin subtypes 1 and 4 are of major interest in the pathogenesis of IIH, although no definite association has been found to date.¹⁰⁰ In addition to its effects on the kidneys, the mineralocorticoid aldosterone is also active on epithelial cells of the choroid plexus, serving to enhance the activity of the Na⁺/K⁺-ATPase exchanger on the luminal membrane.¹⁰¹ Enhanced Na⁺ passage into the CSF results in increased CSF production. As yet there is no direct evidence of increased CSF production in cases of hyperaldosteronism, although aldosterone is found in the CSF in levels correlating to plasma aldosterone and has a known effect on the regulation of CSF volume.^{101,102} Familial cases of IIH suggest a genetic component, which is being further explored in the IIHTT.^{103,104}

Atypical Cases

Because there is no specific diagnostic test for PTCS, exceptions to the diagnostic criteria are reported. “IIH without papilledema,” previously mentioned, is perhaps the most common.^{20,105–107} The largest series of IIHWOP included 25 patients in a large headache center with refractory chronic daily headaches, normal neuroimaging, and an elevated CSF pressure.²⁰ Review of the data presented indicates that 80% of the patients were overusing analgesics. Various analgesics may affect CSF pressure. Alternatively, the patients may have been tense, in pain, or performing a Valsalva maneuver during the LP that would elevate their CSF pressure.⁷⁰ Among 353 IIH patients seen at a neuro-ophthalmology center, only 5.7% of patients had IIHWOP.⁴⁷ Compared with patients with papilledema, they tended to have lower CSF pressures, higher rates of nonphysiologic (“functional”) visual loss, a longer duration of symptoms before diagnosis, and a poor response to conventional PTCS treatments.⁴⁷

“Normal-pressure” PTCS has been reported in a patient who had otherwise typical signs and symptoms of PTCS, including papilledema.¹⁰⁸ The 2013 diagnostic criteria allow for a diagnosis of “probable” PTCS in such cases. Seven patients with clinical features of IIH, elevated CSF pressure, and CSF pleocytosis showed no evidence of another systemic process after a 3- to 10-year follow-up interval; the cause of the pleocytosis is uncertain.¹⁰⁹

Headache and elevated LP opening pressure are inadequate to make the diagnosis of PTCS, because they are nonspecific. Of 168 patients who had an LP in the emergency department to evaluate a chief complaint of headaches, 28 had an opening pressure measured.⁷⁰ It ranged from 85 to 370 mm of CSF. Pressures greater than 200 mm water were found in 14 patients, 10 of whom had a pressure greater than 250 mm water. None had other features of IIH, and all patients were discharged from the emergency department with a diagnosis of benign headache disorder. A more recent study using evoked acoustic emissions to measure CSF pressure noninvasively in patients with migraine found significantly increased pressure during a migraine attack compared with the interictal period.¹¹⁰ Thus, elevated CSF pressure may be a marker of headache in some patients and an isolated CSF pressure measurement is not sufficient to make or exclude a diagnosis of PTCS; the results of the LP must be combined with the other clinical features.

Associated Conditions and Differential Diagnosis

There are many conditions associated with PTCS, some fairly well substantiated and others in isolated case reports. These conditions are listed in **Box 3**. Weight gain and obesity are the only risk factors that have been demonstrated in case-control studies.^{111,112} The major differential diagnoses are meningeal invasion of tumor and venous sinus thrombosis.

Many women with PTCS also have orthostatic edema, a benign condition characterized by abnormal sodium or water retention in the upright posture.¹¹³ Elevated arginine vasopressin levels have been found in both disorders.^{114–117} Most subjects in the IIHTT were at high risk for obstructive sleep apnea using a standard screening questionnaire (Wall M, and the IIHTT Study Group, submitted for publication.).

TREATMENT

PTCS is best managed using a team approach (**Fig. 14**). The neurologist is generally in the best position to direct the management of the patient in collaboration with the ophthalmologist, neurosurgeon, and primary care physician. **Fig. 11** provides an algorithm of general management principles. If the major problem is headache and the patient has good vision, then medical management is appropriate. The goal is to treat the symptoms and the visual function, rather than basing therapy solely on the appearance of the optic nerves. The IIHTT is a multicenter, randomized, double-masked placebo-controlled trial of a supervised dietary program plus acetazolamide or matching placebo tablets for the treatment of patients with IIH and mild visual loss (perimetric mean deviation -2 to -7 dB).¹⁰⁴ The results of the IIHTT will be released in 2014, providing the first evidence-based recommendations for treatment.

MEDICAL MANAGEMENT

Diet and Weight Loss

Weight loss is advocated for obese patients. In one study, 8 morbidly obese women with IIH achieved weight loss (58 ± 5 kg) by gastric surgery.¹¹⁸ They all had resolution of papilledema and improvement in headaches and pulsatile tinnitus with long-term

Box 3**Associated conditions***Obstruction to venous drainage*Cerebral venous sinus thrombosis^{62,81,83}Aseptic (hypercoagulable state)¹⁷³

Septic (middle ear or mastoid infection)

Bilateral radical neck dissection with jugular vein ligation

Jugular vein tumor^{187,188}

Superior vena cava syndrome

Brachiocephalic vein thrombosis¹⁸⁸

Increased right heart pressure

Following embolization of arteriovenous malformation¹⁸⁹*Endocrine disorders*Addison disease¹⁹⁰

Hypoparathyroidism

Obesity, recent weight gain¹¹¹Orthostatic edema¹¹³*Exogenous agents*Amiodarone^{191,192}Cytarabine¹⁹²

Chlordecone (kepone)

Corticosteroids (particularly withdrawal)^{124,193,194}Cyclosporine¹⁹⁵Growth hormone^{196–200}Leuporelin acetate (LH-RH analogue)²⁰¹Levothyroxine (children)^{202,203}Lithium carbonate²⁰⁴Naladixic acid^{205,206}Levonorgestrel (Norplant)^{184,207,208}*Sulfa antibiotics*Tetracycline and related compounds^{209–218}Minocycline^{219–222}Doxycycline²²³Vitamin A^{211,224–226}

Vitamin supplements, liver

Cis-retinoic acid (Accutane)^{211,227–231}*All-trans*-retinoic acid (for acute promyelocytic leukemia)^{232–235}*Infectious or Postinfectious*HIV infection^{236–238}Lyme disease²³⁹

Following childhood varicella^{240,241}

Other medical conditions

Antiphospholipid antibody syndrome^{242–244}

Behçet disease^{245–247}

Occult craniosynostosis²⁴⁸

Polycystic ovary syndrome²⁴⁹

Sarcoidosis²⁵⁰

Obstructive sleep apnea^{251–253}

Systemic lupus erythematosus^{254,255}

Turner syndrome²⁵⁶

follow-up. Postoperative CSF pressures normalized when measured between 4 months and 6 years after surgery. Another retrospective analysis of 58 women with IIH showed that papilledema grade and visual fields improved more rapidly in those losing at least 2.5 kg over a period of 3 months.¹¹⁹ The final visual acuity and visual field were independent of weight loss. Headache and CSF pressure were not quantified in this study. A study of 15 female patients treated with acetazolamide and weight loss correlated a 6% weight loss with resolution of their papilledema and the authors questioned the effectiveness of acetazolamide in this cohort.¹²⁰ Because IIH is frequently associated with orthostatic fluid retention,¹¹³ salt and fluid restriction are also recommended.

Medications

Traditional therapy uses diuretics, particularly carbonic anhydrase inhibitors. Carbonic anhydrase, present in the choroid plexus, has a major role in the secretion of CSF. One study showed that acetazolamide was effective in 75% of patients with PTCS.¹²¹ The effective dose is 1 to 4 g daily in divided doses. Almost all patients taking acetazolamide experience paresthesias, an unpleasant taste with carbonated beverages, altered taste of food, and a low serum bicarbonate level. Severe reactions include allergic rash, aplastic anemia, and renal stones. Acetazolamide and most other diuretics contain a sulfonamide moiety that differs from that of sulfa antibiotics. Thus, sulfa allergy is not a contraindication to acetazolamide treatment.¹²² Methazolamide may be considered in patients who cannot tolerate acetazolamide.

Furosemide reduces CSF secretion in the choroid plexus in addition to its loop diuretic effect. Other diuretics, including thiazides, spironolactone, and triamterene, have been tried with varying success.¹²³ Spironolactone and triamterene can be used in the setting of acetazolamide allergy. Diuretics before a planned period of recumbency are usually helpful in controlling the symptoms of orthostatic edema.¹¹³

Corticosteroids will rapidly decrease the intracranial pressure but are not suitable for chronic use. Their side effects of weight gain and fluid retention are undesirable and counterproductive. Moreover, patients may experience rebound intracranial hypertension as the dose is tapered.¹²⁴ Corticosteroids are generally reserved for the short-term, urgent treatment of patients with visual loss, used in conjunction with a surgical procedure.¹²⁵

The headaches of PTCS can often be managed with medications and techniques that are used in the treatment of migraine. Many of the prophylactic headache

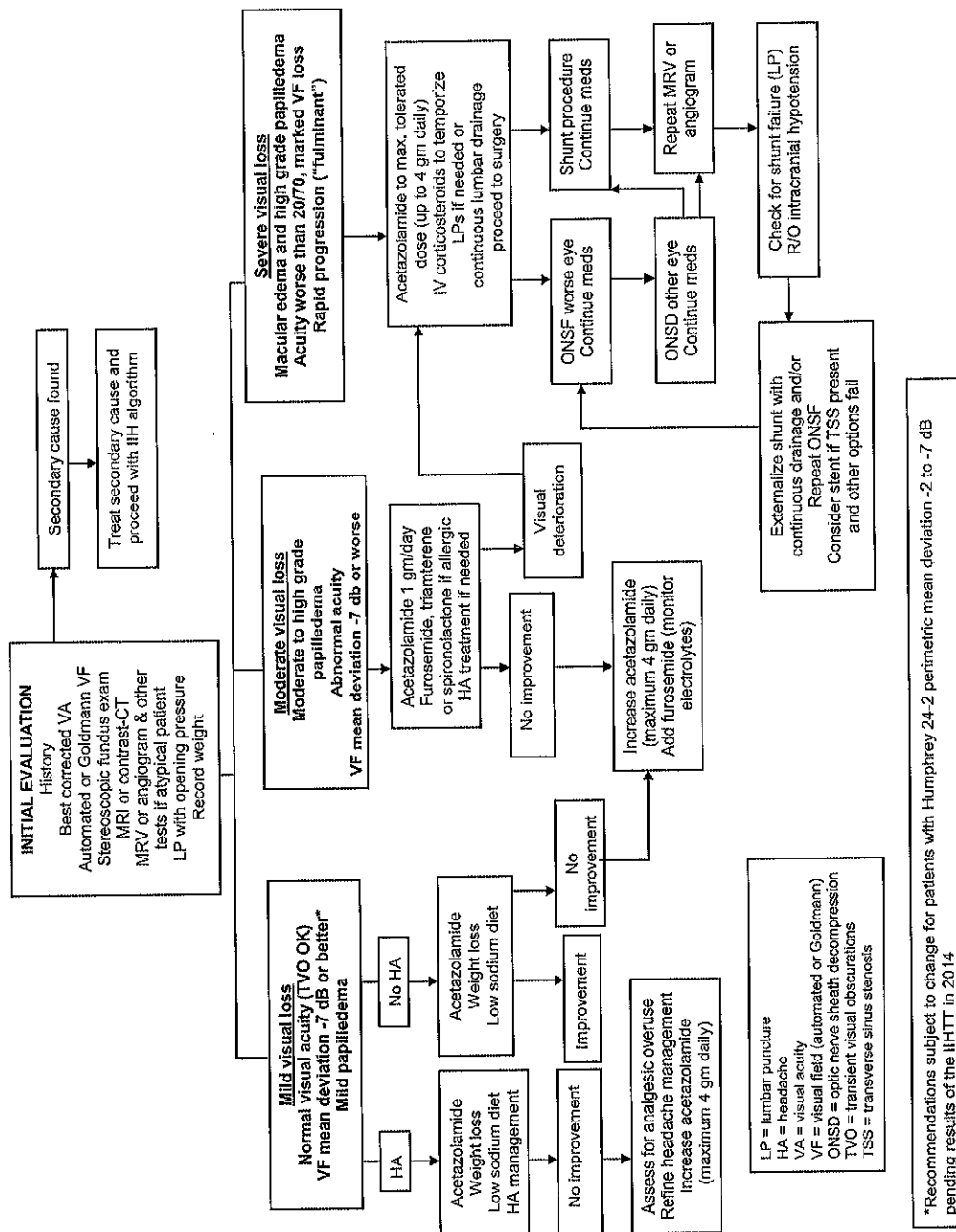


Fig. 14. General treatment algorithm for PTCS. Monitoring of vision with best-corrected acuity and perimetry is imperative because patients may transition between categories.

medications have undesirable side effects in IIH and patients must be monitored carefully while taking them. For example, tricyclic antidepressants and sodium valproate often cause weight gain. Calcium channel blockers carry the potential side effect of peripheral edema. β -Blockers may induce or worsen depression and add to the lethargy caused by acetazolamide. Topiramate is useful for headache prevention and often produces weight loss that is a desirable side effect in most patients with PTCS. In a retrospective review of 24 patients using topiramate during their course of treatment of PTCS, 4 patients did not tolerate it, 15 experienced weight loss, and 10 had improvement in their headaches.¹²⁶ An open-label study comparing acetazolamide and topiramate for treatment of IIH found improvement in both groups with respect to visual field change, and no significant differences between groups.¹²⁷ The role of topiramate as a primary treatment of PTCS is unsubstantiated. Nonsteroidal anti-inflammatory medications may be useful on an intermittent basis. However, patients often self-medicate with over-the-counter pain relievers and may confuse the clinical picture with a superimposed MOH.²⁰ Indomethacin lowers CSF pressure¹²⁸ and does not produce MOH. The triptans and dihydroergotamine may be helpful in patients with concomitant migraine headaches.¹⁹

Repeated LPs are occasionally useful, particularly if patients have infrequent exacerbations of their symptoms. Because they are painful and technically difficult to perform on obese individuals, they are not routinely recommended.

SURGICAL TREATMENT

Surgery is indicated for visual loss or worsening of vision that is attributable to papilledema. The 2 surgical treatments are optic nerve sheath fenestration (ONSF) and shunting. These procedures are not recommended to treat headache alone. The decision to perform one or the other depends on the availability of an orbital surgeon and the status of the patient. Because reported cases include patients who had shunt surgery for intractable headaches, rather than visual loss, it is difficult to compare the efficacy of the 2 procedures for restoring vision. Either procedure may fail, necessitating the use of the other.^{129–131} There have been no prospective, randomized trials of surgical treatments. A comprehensive review of the literature supported ONSF as the preferred treatment of visual loss from IIH, perhaps because visual outcomes were better documented with this procedure.¹³²

ONSF

ONSF performed by a lateral or medial orbital approach or through a lid crease incision, involves fenestrating the optic nerve sheath or opening a “window” in the sheath of an edematous optic nerve.¹³³ Most neuro-ophthalmologists consider ONSF the treatment of choice for patients with failing vision. Its mechanism is not well understood. Some consider it a filtering procedure,¹³⁴ while others contend that the resultant perineuronal scarring shifts the pressure gradient posteriorly from the lamina cribrosa to the myelinated portion of the optic nerve.^{133,135} The procedure likely increases blood flow to the optic nerve as demonstrated by color Doppler imaging preoperatively and postoperatively.^{136,137} Patients in whom vision improved postoperatively had improvement in color Doppler parameters. ONSF should also be considered when severe papilledema extends into the macula. Macular exudates may improve after ONSF.¹³⁸ Pigment mottling and macular scars often persist following surgery, although they are often visually insignificant.¹³⁸

Because headaches are sometimes relieved after ONSF, it is postulated that ONSF produces a global decrease in ICP in some cases,¹³⁹ presuming continuity

between the perineural subarachnoid space and the intracranial subarachnoid space. There is likely much individual variation in this regard. The optic nerve sheath diameter and CSF pressure had a linear relationship within the 15- to 30-mm Hg range in humans participating in CSF absorption studies, with different slopes across subjects. In measures greater than 30 mm Hg, the optic nerve sheath diameter remained constant.¹⁴⁰

ONSF is generally effective, but sometimes requires revision.^{141,142} ONSF tends to be more effective in acute papilledema than chronic papilledema¹⁴² and is not indicated once the papilledema has resolved. Studies show that bilateral improvement in vision often occurs after a unilateral procedure.^{143,144} The complications of ONSF include failure, ischemic optic neuropathy, transient diplopia, and transient blindness.¹⁴⁵

CSF Shunting

Because the ventricles are not enlarged in PTCS, lumboperitoneal shunting was previously preferred over ventriculoperitoneal (VP) shunting. Shunts are often quite effective in the short term but some patients require multiple revisions.^{146–149} One study reviewed the efficacy of lumboperitoneal and VP from 6 institutions, where 37 patients underwent a total of 73 lumboperitoneal shunts and 9 VP shunts.¹⁵⁰ Only 14 patients were “cured” after a single surgical procedure. The shunt failure rate was high, and 27 shunts were replaced within 2 months.

Another retrospective review of 30 patients showed 82% overall improvement of symptoms (headache, diplopia, transient visual obscurations) with resolution of symptoms in 29%.¹⁵¹ Most patients had improvement or stabilization of the visual field. There was a high revision rate (126 revisions; range 0–38 revisions per patient). There was no association between early shunt durability and the long-term need for multiple revisions; patients requiring more than 3 revisions were more likely to need additional shunt procedures.

Overall, the lumboperitoneal shunt failure rate is approximately 50% in PTCS.^{147,149,150,152,153} The most common reasons for revision are shunt obstruction, intracranial hypotension, and lumbar radiculopathy. Visual deterioration may be the only sign of shunt failure and may occur even if the shunt is functioning.^{154,155} Other complications include infection, abdominal pain, CSF leak, hindbrain herniation headaches, and migration of the peritoneal catheter.^{149,156,157} Intracerebral hematoma occurs rarely.¹⁵⁸ Cisterna magna shunting avoids the problems of low-pressure headaches and radiculopathy but is a more extensive procedure with a significant failure rate.¹⁵⁹ There is renewed enthusiasm for VP shunts, which may be inserted quite accurately using stereotactic techniques.^{163,160} The effect of shunting on CSF production is unknown.

Bariatric surgery may be an option for the long-term management of morbidly obese patients but is not helpful for acute management.¹¹⁸ It may also confer additional health benefits in these patients who face considerable life-long medical morbidity from their obesity.

Venous Sinus Stenting

The discovery of transverse sinus stenosis in association with IIH prompted endovascular stenting as a treatment for the disorder. Numerous case series have been reported, with variable criteria for stenting and generally positive results.^{161–166} Unfortunately, considerable morbidity has also occurred including subdural hematoma, epidural hematoma, anaphylaxis, hearing loss, and death.¹⁶⁷ Given that transverse sinus stenosis does not seem to affect the clinical course of IIH,^{168,169} stenting should

be reserved for patients with severe or fulminant disease who have exhausted other surgical methods.

SPECIAL CIRCUMSTANCES

Pregnancy

Although IIH may develop or worsen in pregnancy, its occurrence rate in pregnancy is similar to age-matched nonpregnant controls.⁸⁷ There is no increased risk of fetal loss in these patients, and therapeutic abortion is not indicated.⁸⁷ The diagnostic criteria of IIH during pregnancy is no different than for the general population. The management of active PTCS in a pregnant woman can be challenging, but most patients do well, with little or no permanent visual loss.¹⁷⁰ Most patients can be managed conservatively with careful neuro-ophthalmic follow-up and repeated LPs. Acetazolamide may be used after 20 weeks' gestation.¹⁷¹ Thiazide diuretics and tricyclic antidepressants are generally avoided. If vision deteriorates, corticosteroids may be used. There is no contraindication to ONSF or shunting during pregnancy, although there is a theoretical risk of LP shunt malfunction from peritoneal catheter obstruction with the enlarging uterus.¹⁷² PTCS arising in the postpartum period or following fetal loss raises the suspicion of cerebral venous thrombosis.¹⁷³

Children and Adolescents

PTCS occurs with equal frequency in boys and girls before puberty.^{7,8,174} In adolescents, girls are more often affected than boys.⁷ Obesity is not as prevalent in young children as in adolescents and adults, and a secondary cause of intracranial hypertension is identifiable in approximately 50% of cases.^{9,175,176} The most commonly predisposing conditions are otitis media, viral infection, medications, and closed head trauma.¹⁷⁷ It is possible that antibiotic use is underestimated as a precipitating factor, because all children with otitis media and many with viral infections are treated with antibiotics. The presenting signs of PTCS in young children are stiff neck, strabismus, irritability, apathy, somnolence, dizziness, and ataxia.^{175,178} If the fontanelles are open and patent, papilledema may be absent.^{174,178} Focal signs including lateral rectus palsy, facial palsy, and torticollis seem to be more common in children than adults.¹⁷⁸⁻¹⁸¹ If the precipitating cause is addressed, the disorder is generally benign and short-lived. However, permanent visual loss may occur, particularly if there is an associated dural venous sinus thrombosis.¹⁷⁹ The treatment is similar to management in adults.^{174,182,183}

PTCS with an Identified Secondary Cause

Withdrawal of the causative agent or treatment of the underlying cause is imperative but neither guarantees rapid reversion of CSF pressure to normal nor reversal of symptoms and signs.¹⁸⁴ Medical and surgical treatments are used as clinically indicated to prevent permanent visual loss.

Fulminant PTCS

There is a small subgroup of patients who experience a rapid onset of symptoms and precipitous visual decline. They often have significant visual field loss, central visual acuity loss, and marked papilledema at presentation.¹⁸⁵ Macular edema or ophthalmoparesis may also be present. A progressive or "malignant" course requires rapid and aggressive treatment. A multidisciplinary physician team and one or more surgical procedures are usually required. Other therapeutic measures include intravenous corticosteroids, intravenous acetazolamide, and insertion of a

lumbar drain. Cerebral venous sinus thrombosis is an important diagnostic consideration in these patients.

EVALUATION, ADJUSTMENT, AND RECURRENCE

Although headaches may persist indefinitely, most patients with PTCS have a monophasic course illness with remission. Re-evaluation and visual monitoring are most frequent in the acute to subacute stages. Depending on the visual status and tempo of visual decline, daily or weekly monitoring may be needed in the acute phases. As the patient's vision stabilizes and the papilledema remits, the interval between monitoring visits may be gradually extended, and many neuro-ophthalmologists advocate life-long yearly monitoring once the disorder remits. Retinal nerve fiber layer gliosis may prevent the resolution of optic disc elevation in some patients. IIH may recur with weight gain¹⁸⁶ and unwitting exposure to a provoking medication may incite recurrence in patients with medication-induced IIH. Papilledema may not be robust with a recurrence and may be absent following ONSF or with optic atrophy.

SUMMARY

IIH is officially considered a "rare" disorder by the National Institutes of Health but the incidence is rising. A primary care physician, an urgent care facility, or the emergency department is often the patient's first point of contact in the medical system. Even those with visual symptoms may not see an ophthalmologist or optometrist initially, particularly if their pain is severe. There is considerable variability in the presentation, making it imperative to measure the visual acuity and perform fundoscopy in all patients with headaches, particularly if they fit the typical demographic for IIH. Evaluation by an ophthalmologist is imperative to assess the vision, perimetry, and status of the optic nerve appearance at diagnosis and throughout the course of disease. Medical and surgical treatment options are used, depending on the visual status of the patient, the tempo of visual loss, and the availability of the appropriate surgical specialist. In some circumstances, patients who present with visual acuity loss or pronounced visual field loss may be best managed at a tertiary center with access to a neuro-ophthalmologist and specialty surgical care. Most patients with PTCS have a good outcome but a small percentage is left with legal or complete blindness and the associated devastating consequences.

The IIHTT is an important step not only in determining evidence-based guidelines for treating patients with mild vision loss but also in understanding the disease process. The published results will be available in 2014. The IIH Study Group is proposing a prospective, randomized surgical trial to provide evidence-based guidelines for treating patients with moderate to severe vision loss. It is hoped that during the next decade, significant advances will be made toward the understanding and treatment of this disorder.

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